



68° CONGRESSO NAZIONALE SIGG

Ritorno al futuro

FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI



BIOMARCATORI DI CAPACITÀ INTRINSECA

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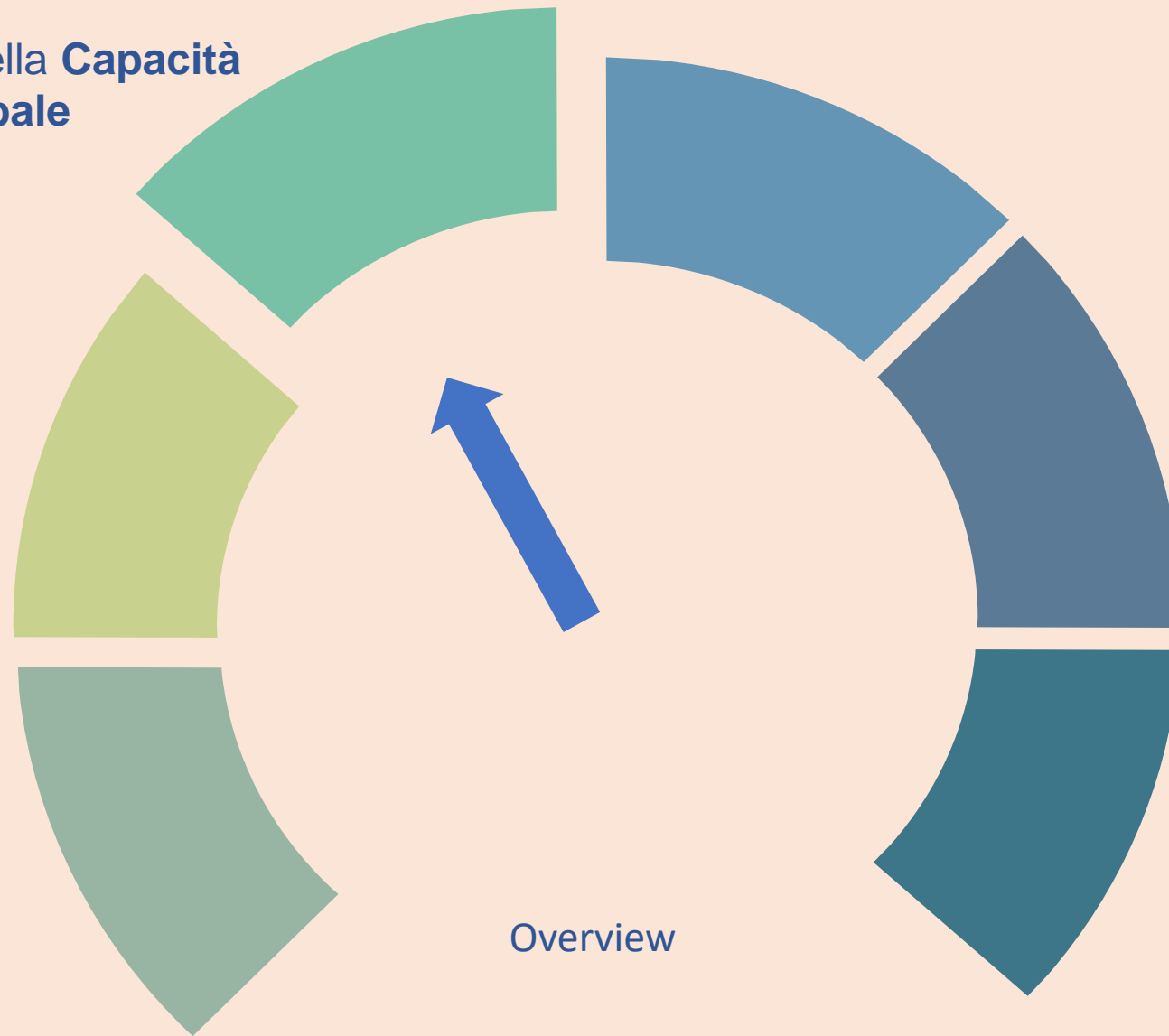


Biomarcatori della **Capacità Intrinseca globale**

Interazioni tra domini e marcatori clinici

Domini della **Capacità Intrinseca**

Overview

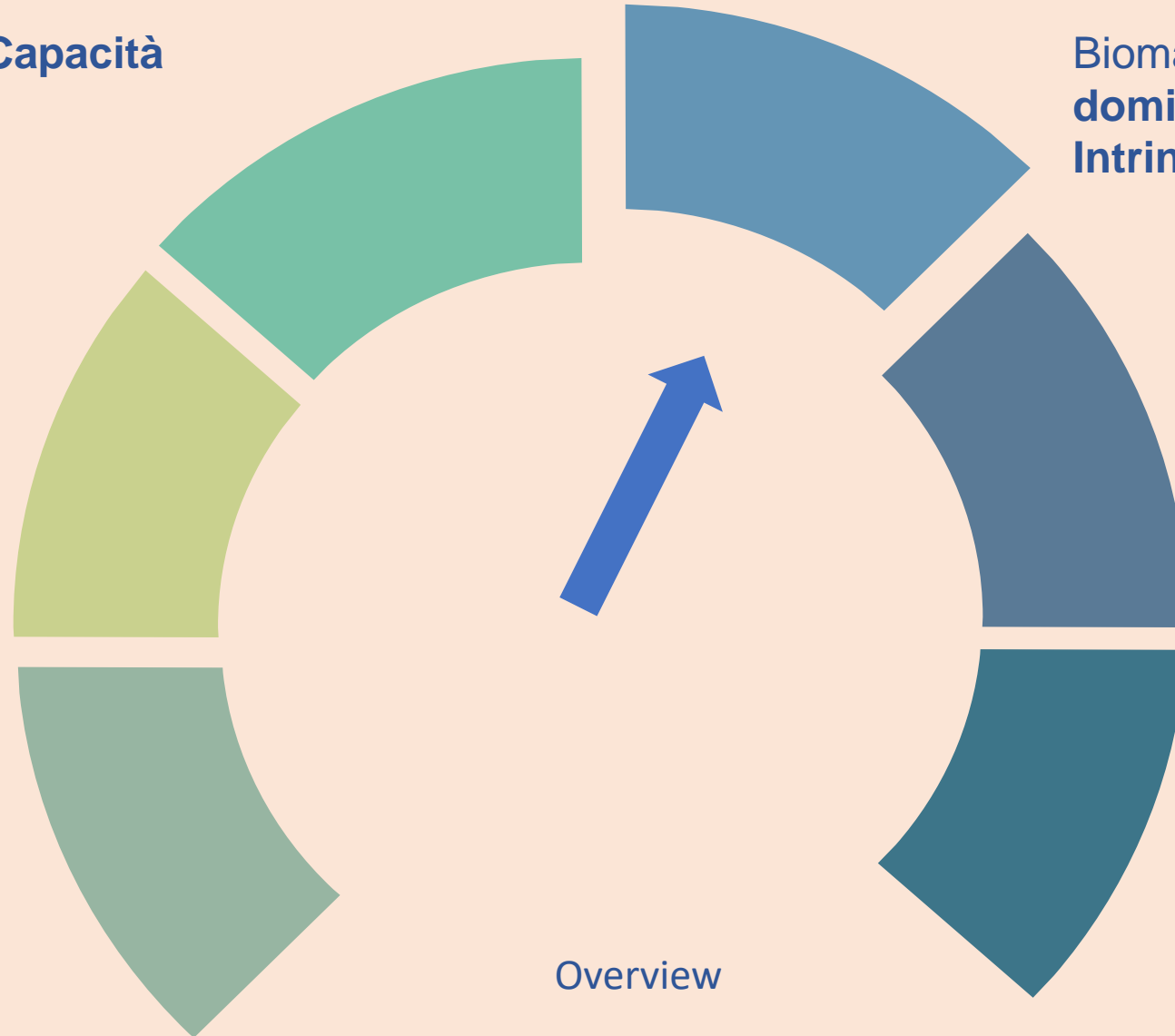




Biomarcatori della **Capacità Intrinseca globale**

Biomarcatori dei **singoli domini della Capacità Intrinseca**

Interazioni tra domini e marcatori clinici



Domini della Capacità Intrinseca

Overview



Biomarcatori della **Capacità Intrinseca globale**

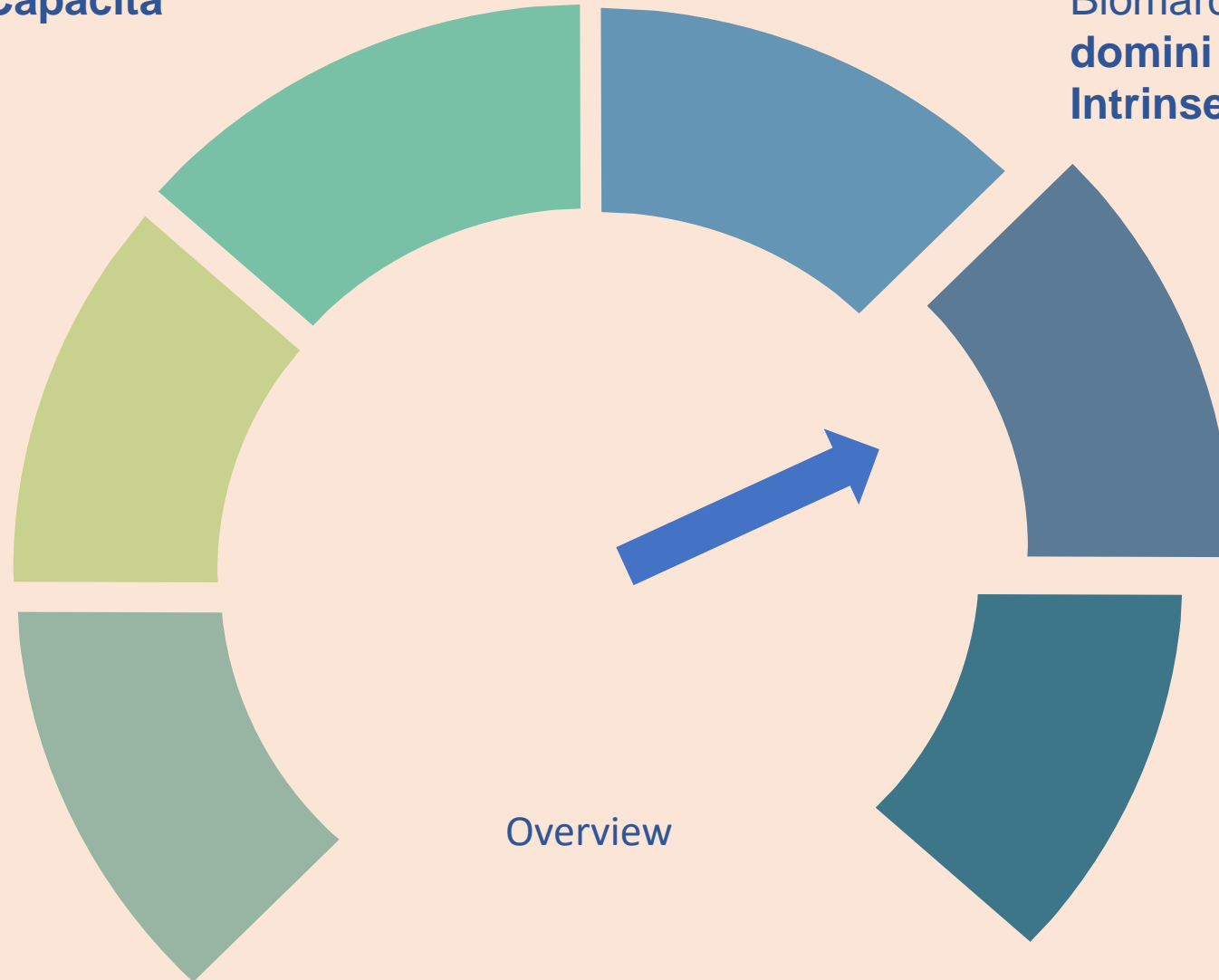
Biomarcatori **dei singoli domini della Capacità Intrinseca**

Biomarcatori delle **Traiettorie della IC**

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Domini della **Capacità Intrinseca**

Overview





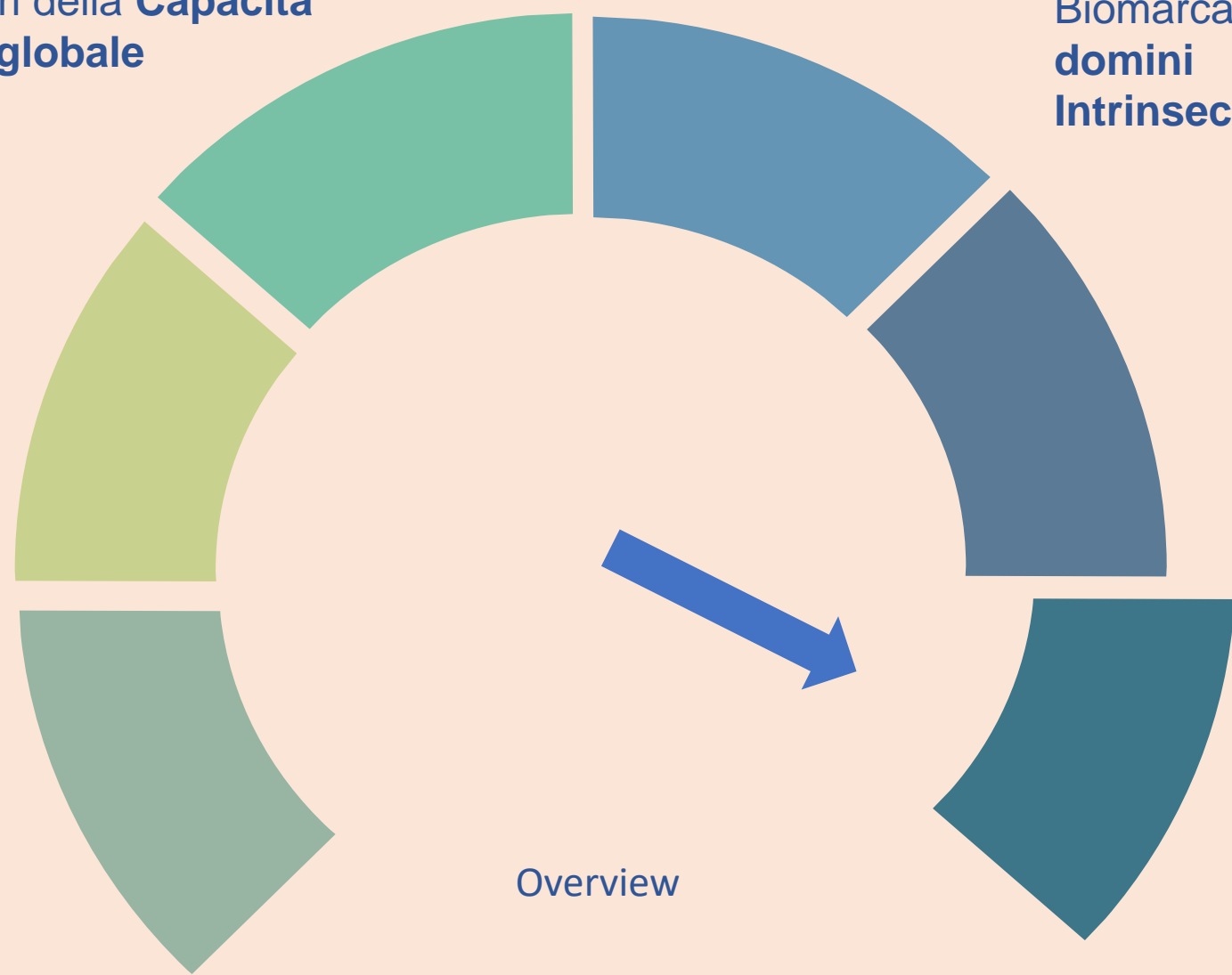
Biomarcatori della **Capacità Intrinseca globale**

Biomarcatori **dei singoli domini della Capacità Intrinseca**

Biomarcatori delle **Traiettorie della IC**

Take home messagesBack to the Future

Overview



Interazioni tra domini e marcatori clinici

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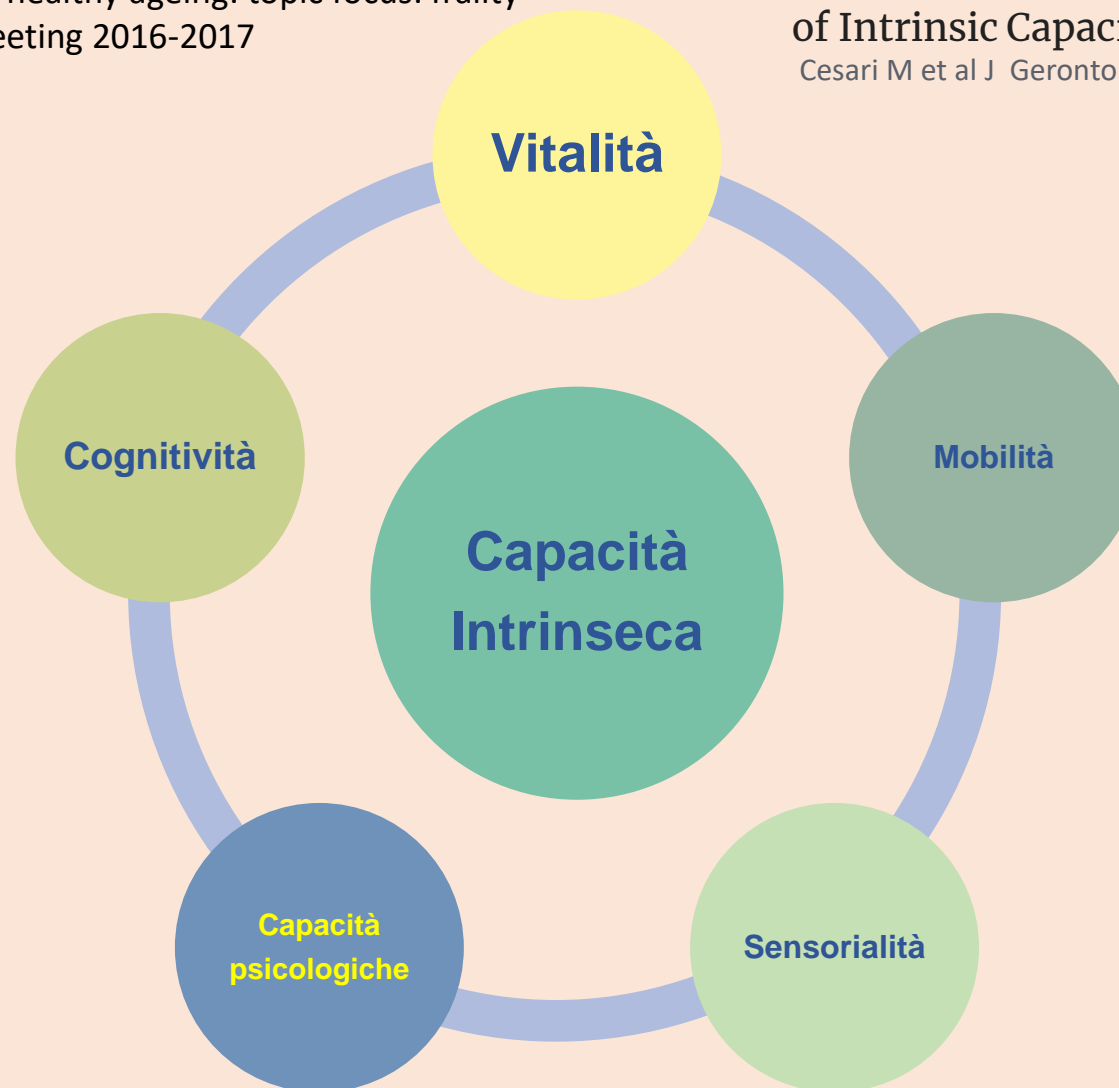
**Capacità
Intrinseca**



Organziation WH. WHO Clinical consortium on healthy ageing: topic focus: frailty and intrinsic capacity: report of consortium meeting 2016-2017

Evidence for the Domains Supporting the Construct of Intrinsic Capacity

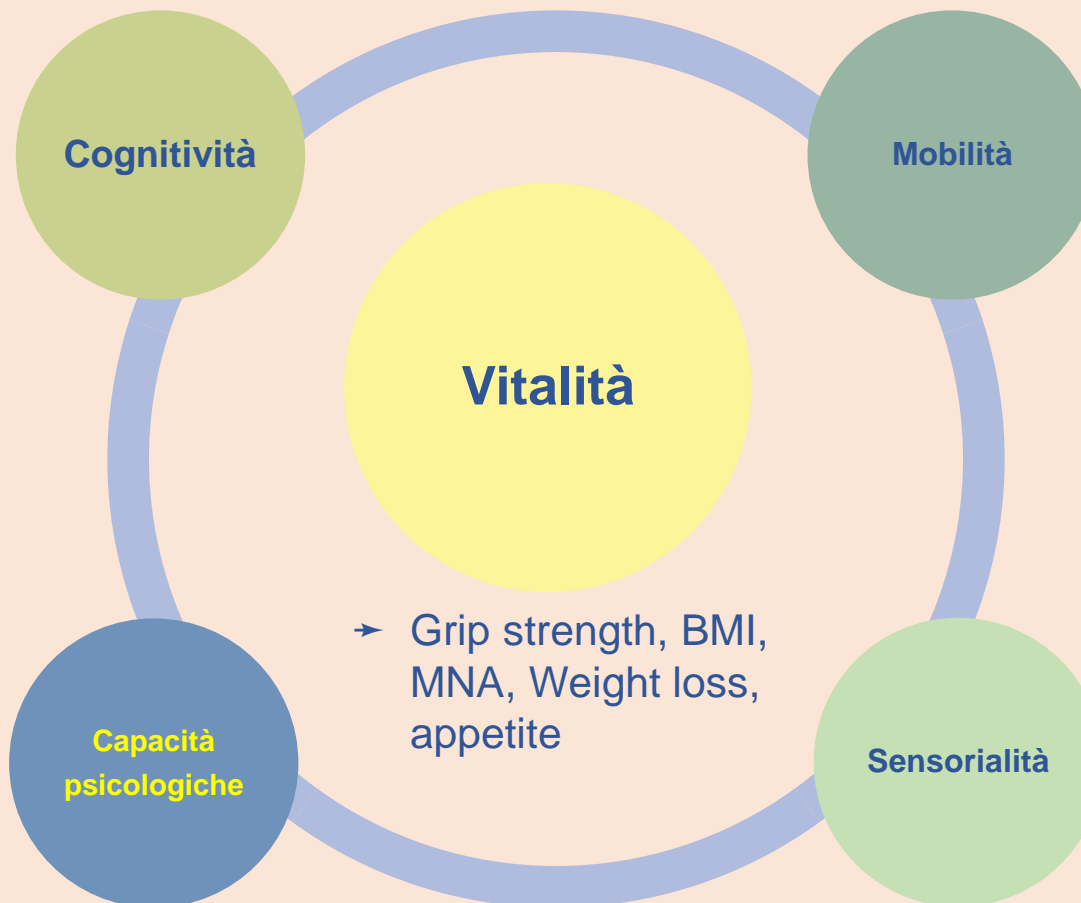
Cesari M et al J Gerontol A Biol Sci Med Sci 2018 Nov 10;73(12):1653-1660.





Clinical markers of IC

➤ **COGNITIVE TESTS:**
MMSE, Recall, Verbal, Letter assessments, Memory test.



➤ SPPB, Gait, Pick pencil, Grip strength

➤ GDS, EuroQol, CES_D, Self report sleep, life satisfaction, social participation

➤ Grip strength, BMI, MNA, Weight loss, appetite

➤ Audiometry, Vision, Whisper test

Adapted from WHO working definition of vitality capacity for healthy longevity monitoring Lancet Healthy Longev 2022 Nov;3(11):e789-e796.



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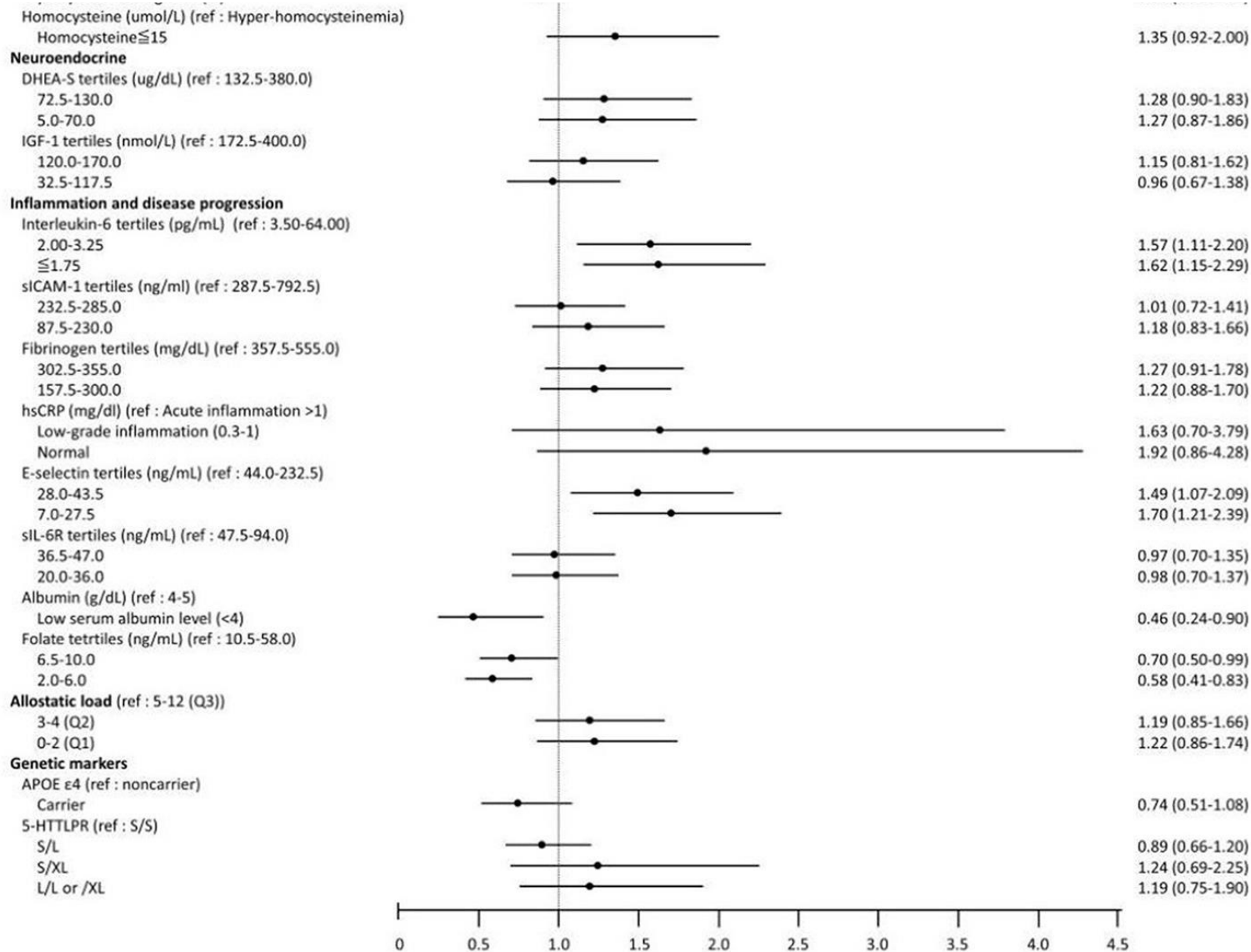
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Biological Features of the Outcome-Based Intrinsic Capacity Composite Scores From a Population-Based Cohort Study: Pas de Deux of Biological and Functional Aging

Published online 2022 Mar 4
doi: [10.3389/fmed.2022.851882](https://doi.org/10.3389/fmed.2022.851882)

- Social Environment & Biomarkers of Aging Study (SEBAS)
n= 839 ≥ 50 anni (età media: 65.3 ± 9.5 anni)
- Formulato e validato un composite score della IC
- Valutare un largo spettro di biomarcatori genetici, metabolici & infiammatori secondo IC
- Esplorare il valore predittivo dei biomarcatori sulle traiettorie della IC sulla mortalità a 4 anni



**≥ 50 anni
(n=839)**



Inflammation and disease progression

Interleukin-6 tertiles (pg/mL) (ref : 3.50-64.00)

2.00-3.25

≤1.75

sICAM-1 tertiles (ng/ml) (ref : 287.5-792.5)

232.5-285.0

87.5-230.0

Fibrinogen tertiles (mg/dL) (ref : 357.5-555.0)

302.5-355.0

157.5-300.0

hsCRP (mg/dl) (ref : Acute inflammation >1)

Low-grade inflammation (0.3-1)

Normal

E-selectin tertiles (ng/mL) (ref : 44.0-232.5)

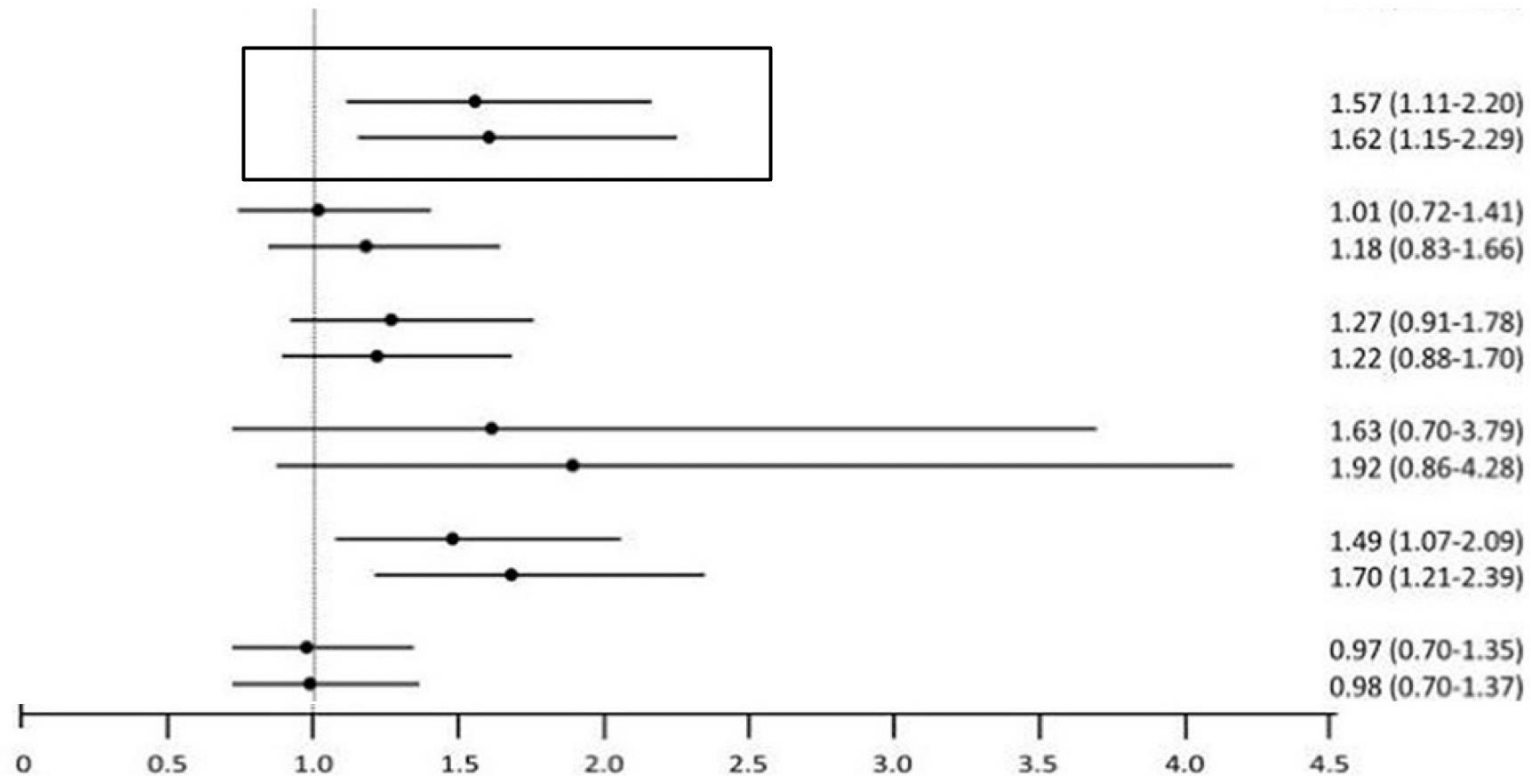
28.0-43.5

7.0-27.5

sIL-6R tertiles (ng/mL) (ref : 47.5-94.0)

36.5-47.0

20.0-36.0



**≥ 50 anni
(n=839)**

Adjusted for age, sex, education, smoking status, socioeconomic status, number of comorbidities



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≥ 60 anni

Inflammation and disease progression

Interleukin-6 tertiles (pg/mL) (ref : 3.50-64.00)

2.00-3.25

≤1.75

sICAM-1 tertiles (ng/ml) (ref : 297.5-792.5)

240.0-295.0

87.5-237.5

Fibrinogen tertiles (mg/dL) (ref : 360.0-555.0)

307.5-357.5

160.0-305.0

hsCRP (mg/dl) (ref : Acute inflammation >1)

Low-grade inflammation (0.3-1)

Normal

E-selectin tertiles (ng/mL) (ref : 44.0-232.5)

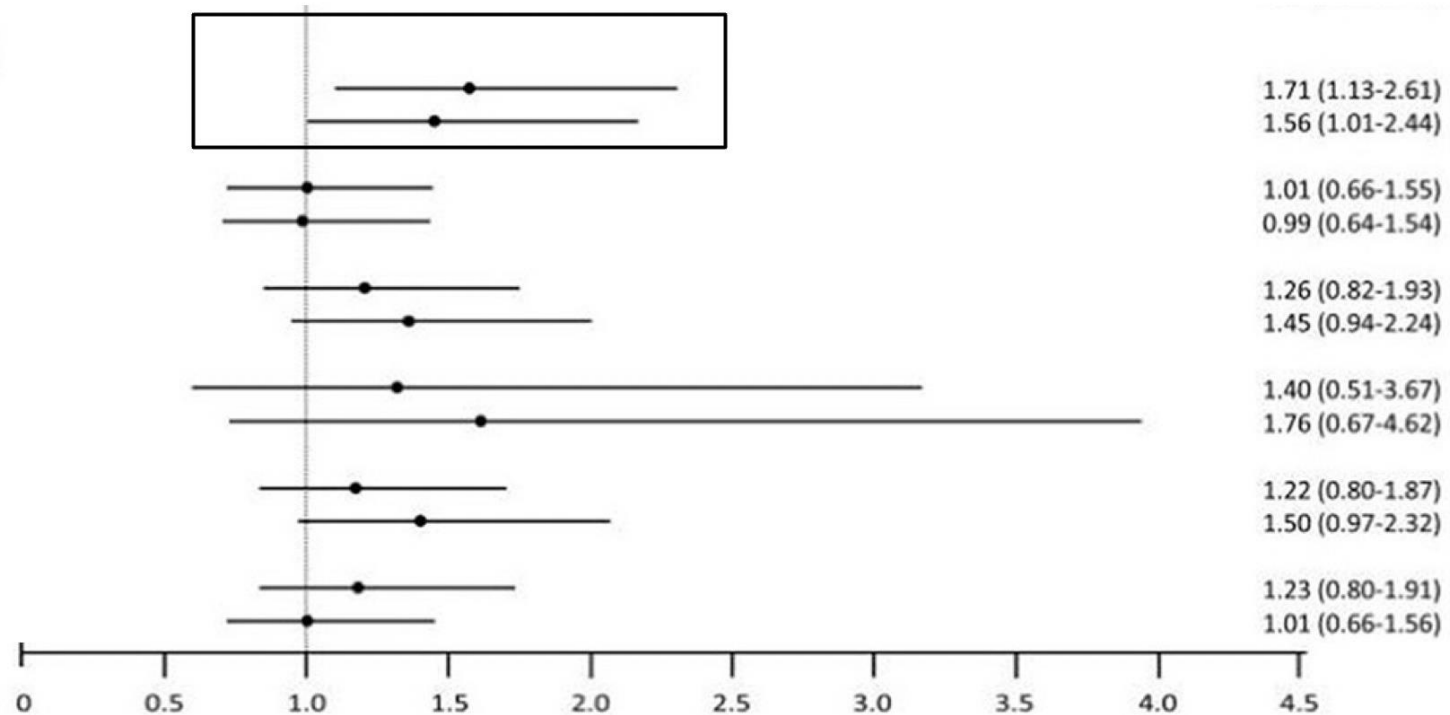
28.0-43.5

7.0-27.5

sIL-6R tertiles (ng/mL) (ref : 49.0-90.0)

37.5-48.5

20.0-37.0

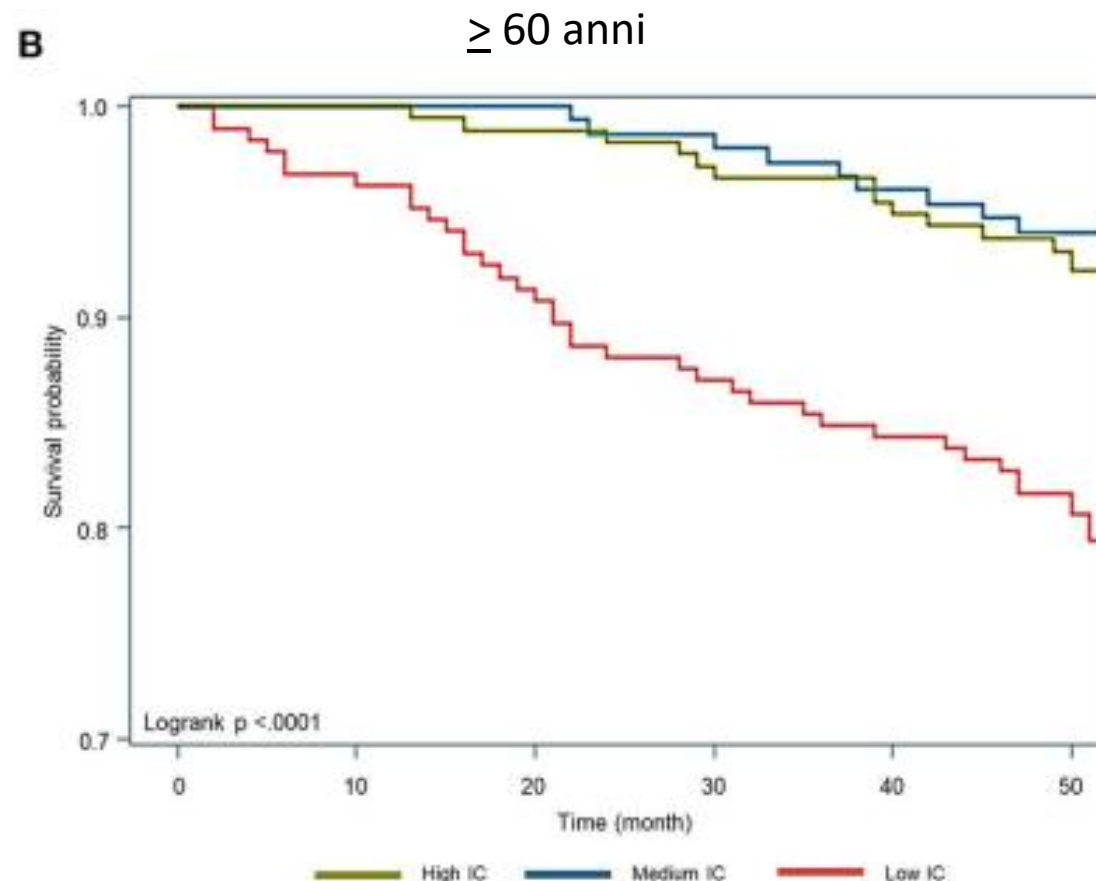
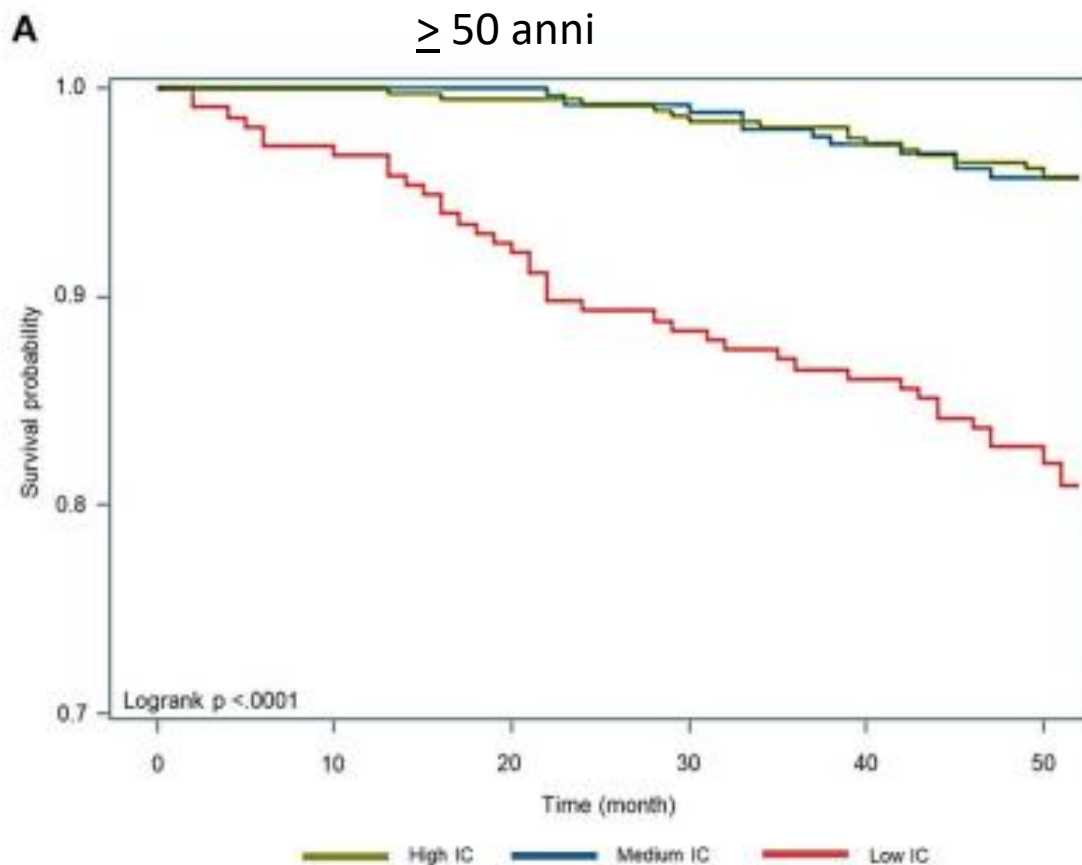


Adjusted for age, sex, education, smoking status, socioeconomic status, number of comorbidities



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Biological Features of the Outcome-Based Intrinsic Capacity Composite Scores From a Population-Based Cohort Study: Pas de Deux of Biological and Functional Aging

	Unadjusted model			Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Total study subjects (aged ≥ 50)									
High IC	<i>ref</i>	–	–	<i>Ref</i>	–	–	<i>ref</i>	–	–
Medium IC	1.05	0.48–2.28	0.91	0.92	0.42–2.03	0.83	0.84	0.38–1.88	0.67
Low IC	4.88	2.69–8.85	<0.01	3.02	1.52–6.00	<0.01	2.50	1.22–5.11	0.01
Subgroup analysis (aged ≥ 60)									
High IC	<i>ref</i>	–	–	<i>ref</i>	–	–	<i>ref</i>	–	–
Medium IC	0.80	0.34–1.87	0.60	0.81	0.34–1.93	0.64	0.73	0.30–1.76	0.52
Low IC	2.89	1.53–5.45	<0.01	2.63	1.30–5.36	<0.01	2.19	1.03–4.64	0.04

HR, Hazard ratio; CI, Confidence interval.

Model 1: adjust for age, sex, level of education, smoking status, socioeconomic status, and number of comorbidities.

Model 2: adjust for age, sex, level of education, smoking status, socioeconomic status, number of comorbidities and biomarkers (e.g., IL-6, E-selectin, albumin and folate for total study subjects; IL-6, albumin, folate and APOE gene for subgroup analysis).



Biological Features of the Outcome-Based Intrinsic Capacity Composite Scores From a Population-Based Cohort Study: Pas de Deux of Biological and Functional Aging

	Unadjusted model			Model 1			Model 2		P-value
Ha formulato e validato una misura di CI globale con un Composite score									
Total study subjects (aged ≥ 50)									
High							ref		
Medi	IL-6 erano associati a livelli di CI migliore				42–2.03	0.83	0.84	0.38–1.88	0.67
Low IC	4.88	2.69–8.85	<0.01	3.02	1.52–6.00	<0.01	2.50	1.22–5.11	0.01
Subarouo analvsis (aaed > 60)									
High	Terzile piu' basso della CI era associato ad un maggiore rischio di mortalità								
Medium IC	0.80	0.34–1.87	0.60	0.81	0.34–1.93	0.64	0.73	0.30–1.70	0.52
Low IC	2.89	1.53–5.45	<0.01	2.63	1.30–5.36	<0.01	2.19	1.03–4.64	0.04

HR, Hazard ratio; CI, Confidence interval.

Model 1: adjust for age, sex, level of education, smoking status, socioeconomic status, and number of comorbidities.

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Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults

Journal of Cachexia, Sarcopenia and Muscle 2023; 14: 930–939

The MAPT (Multidomain Alzheimer Prevention Trial) study

1238 partecipanti (età media 76,2 anni)
63.7% donne

Composite score IC

4 domini (0-60 mesi)

Cognition: MMSE
Locomotion: SPPB
Psychological: GDS-15
Vitality: Grip strength

5 domini (0,12,24 mesi)

Cognition: MMSE
Locomotion: SPPB
Psychological: GDS-15
Vitality: Grip strength
Sensory: Near vision acuity, HHIE-S



Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults

Journal of Cachexia, Sarcopenia and Muscle 2023; **14**: 930–939

L'associazione a baseline dei biomarcatori dell'infiammazione e la Capacità Intrinseca

Plasma biomarker ^a	Four-domain IC score ^b			
	N	β	95% CI	P
Cross-sectional				
CRP	1060	-1.56	-2.64 - -0.48	0.005
IL-6	1062	-3.16	-4.82 - -1.50	<0.001
TNFR-1	1063	-6.86	-10.25 - -3.47	<0.001
MCP-1	1063	1.08	-1.99 - 4.16	0.490
GDF-15	1062	-7.07	-10.02 - -4.12	<0.001

	Five-domain IC score ^c			
	N	β	95% CI	P
	453	-1.13	-2.70 - 0.43	0.156
	460	-2.76	-5.19 - -0.32	0.026
	461	-5.01	-9.99 - -0.02	0.049
	461	0.01	-4.28 - 4.29	0.998
	460	-5.20	-9.48 - -0.92	0.017

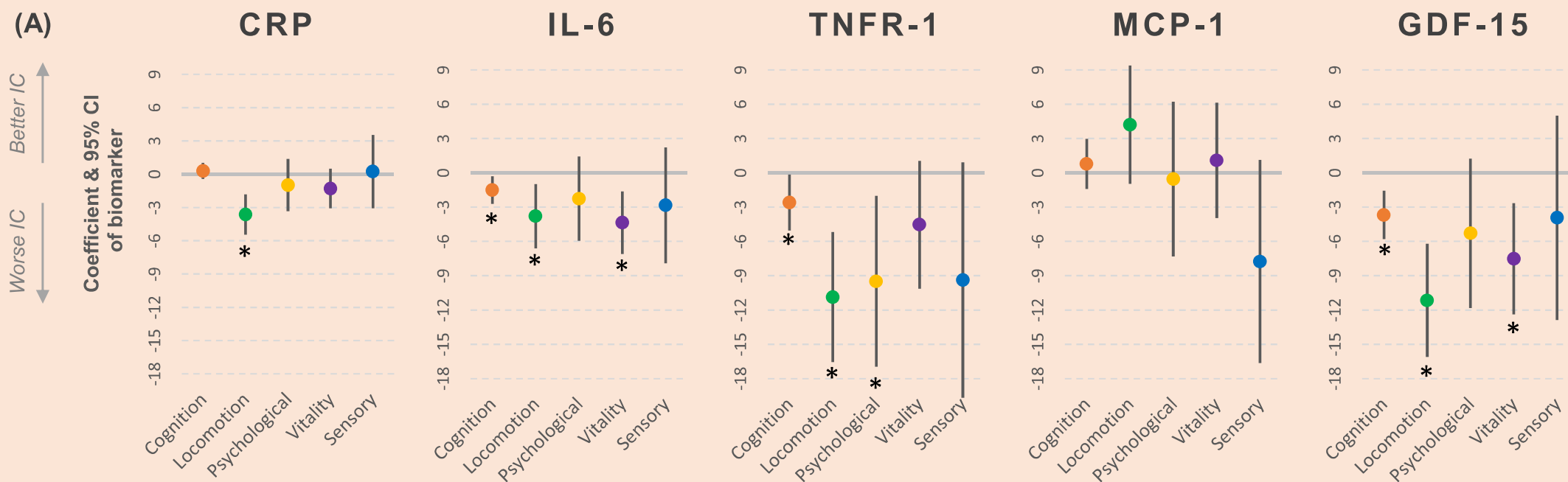
^bComposed of cognitive, locomotive, psychological and vitality domains; evaluated by linear mixed-effects regression with adjustment for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) group allocation and educational level.

^cComposed of cognitive, locomotive, psychological, vitality and sensory (vision + hearing) domains; evaluated by linear mixed-effects regression with adjustment for age, sex, MAPT group allocation and educational level.

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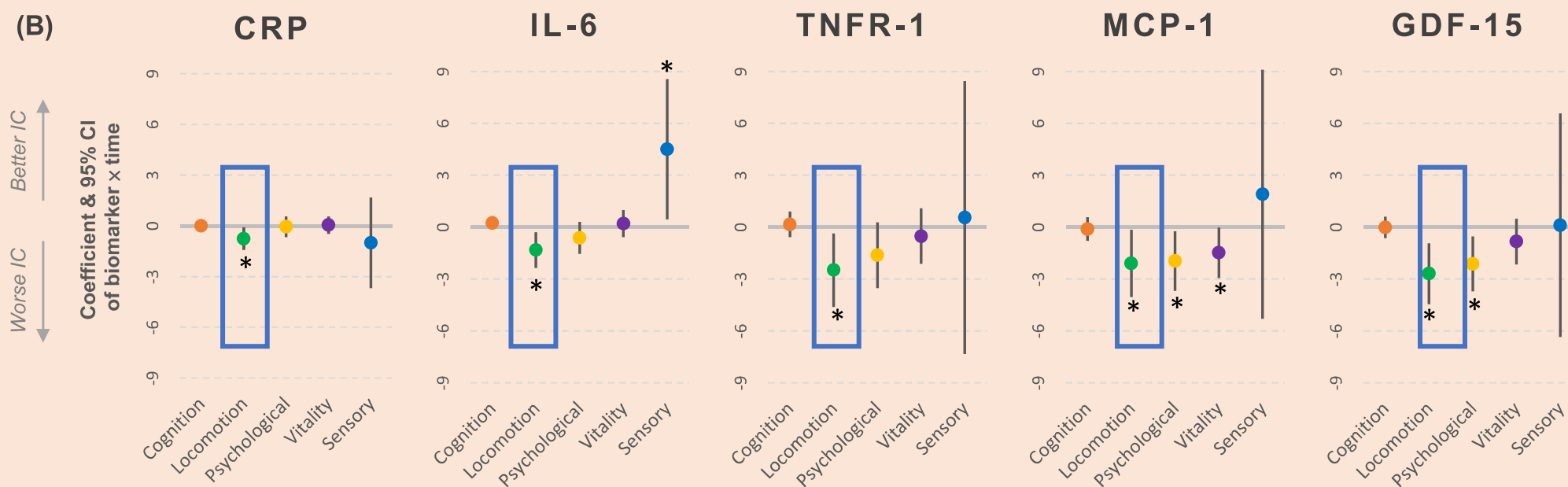
L'associazione a baseline dei biomarcatori con singolo dominio secondo il livello di IC



Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults

Journal of Cachexia, Sarcopenia and Muscle 2023; 14: 930–939

L'associazione longitudinale dei biomarcatori con singolo dominio secondo il livello di IC





Plasma biomarker ^a	Four-domain IC score ^b					Five-domain IC score ^c				
	<i>N</i>	β	95% CI		<i>P</i>	<i>N</i>	β	95% CI		<i>P</i>
Longitudinal										
CRP	1060	-0.13	-0.45	0.19	0.429	453	0.40	-0.96	1.76	0.566
IL-6	1062	-0.36	-0.85	0.13	0.150	460	1.59	-0.52	3.70	0.139
TNFR-1	1063	-1.28	-2.29	-0.27	0.013	461	-2.03	-6.20	2.14	0.341
MCP-1	1063	-1.33	-2.24	-0.42	0.004	461	0.25	-3.52	4.03	0.895
GDF-15	1062	-1.42	-2.26	-0.58	0.001	460	-1.24	-4.66	2.19	0.479

TNFR-1, MCP-1 & GDF-15 correlavano con un declino più veloce della IC nei 4 anni di follow up



Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults

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TRAJECTORIES OF INTRINSIC CAPACITY

Mean (SD)	Whole study population	IC slopes (point per year) ^a			P value for difference ^b	Post hoc analysis ^c
		Accelerated IC decline (lowest 20%, < -1.78)	Slight IC decline (middle 60%, -1.78 to -0.53)	Stable IC (highest 20%, > -0.53)		
IC at baseline, 0–100	78.9 (9.3)	78.2 (8.9)	79.3 (9.4)	78.5 (9.4)	0.512	
IC slopes (change per year)	-1.17 (0.86)	-2.46 (0.68)	-1.10 (0.32)	-0.10 (0.36)	<0.001	* ** ***
Inflammation-related biomarkers						
CRP, mg/L	3.3 (5.2)	3.4 (5.4)	3.4 (5.4)	2.9 (4.6)	0.419	
IL-6, pg/mL	3.9 (12.4)	4.0 (9.6)	4.1 (14.9)	3.2 (3.0)	0.324	
TNFR-1, pg/mL	1223.7 (441.2)	1282.3 (455.6)	1239.8 (459.3)	1119.1 (346.5)	0.001	* ** ***
MCP-1, pg/mL	221.7 (86.2)	231.7 (80.1)	222.5 (88.9)	209.7 (82.6)	0.035	* ** ***
GDF-15, pg/mL	1125.7 (504.9)	1201.7 (550.2)	1145.9 (524.1)	991.8 (356.2)	0.002	* ** ***

CRP, C-reactive protein; GDF-15, growth differentiation factor-15; IC, intrinsic capacity; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; TNFR-1, tumour necrosis factor receptor-1.



Conclusioni

L'utilizzo di un Composite Score della Capacità Intrinseca rappresenta un importante ruolo per la ricerca ma ancora non esiste un valore standard

La ricerca di biomarcatori della Capacità Intrinseca globale, dei singoli domini e delle traiettorie rimane fondamentale per identificare persone a rischio di declino rapido

Back to the future.....
Biomarcatori di infiammazione cronica
Hallmarks of Aging
“oldies but goodies”



Altre Traiettorie di Capacità Intrinseca

GeroScience (2023) 45:3409–3418

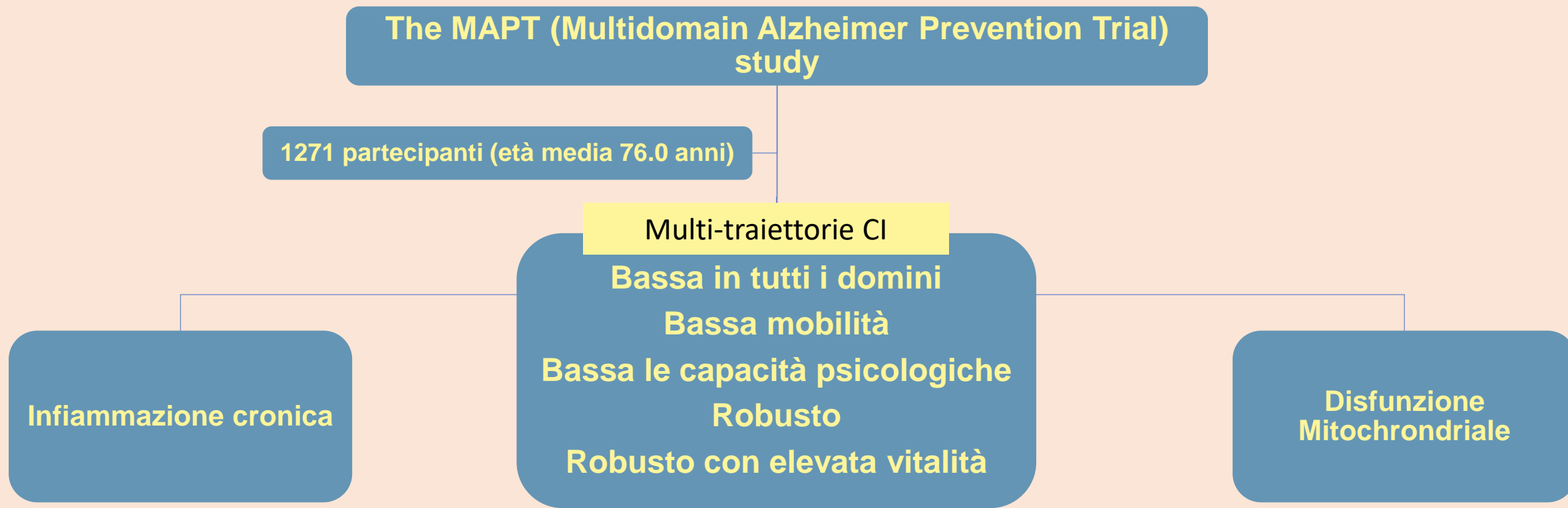
<https://doi.org/10.1007/s11357-023-00906-2>

- Bassa in tutti i domini
- Bassa mobilità
- Bassa le capacità psicologiche
- Robusto
- Robusto con elevata vitalità



Association between aging-related biomarkers and longitudinal trajectories of intrinsic capacity in older adults

GeroScience (2023) 45:3409–3418
<https://doi.org/10.1007/s11357-023-00906-2>





Association between aging-related biomarkers and longitudinal trajectories of intrinsic capacity in older adults

Table 2 Association between plasma biomarkers and IC multi-trajectory groups examining by multinomial logistic regression

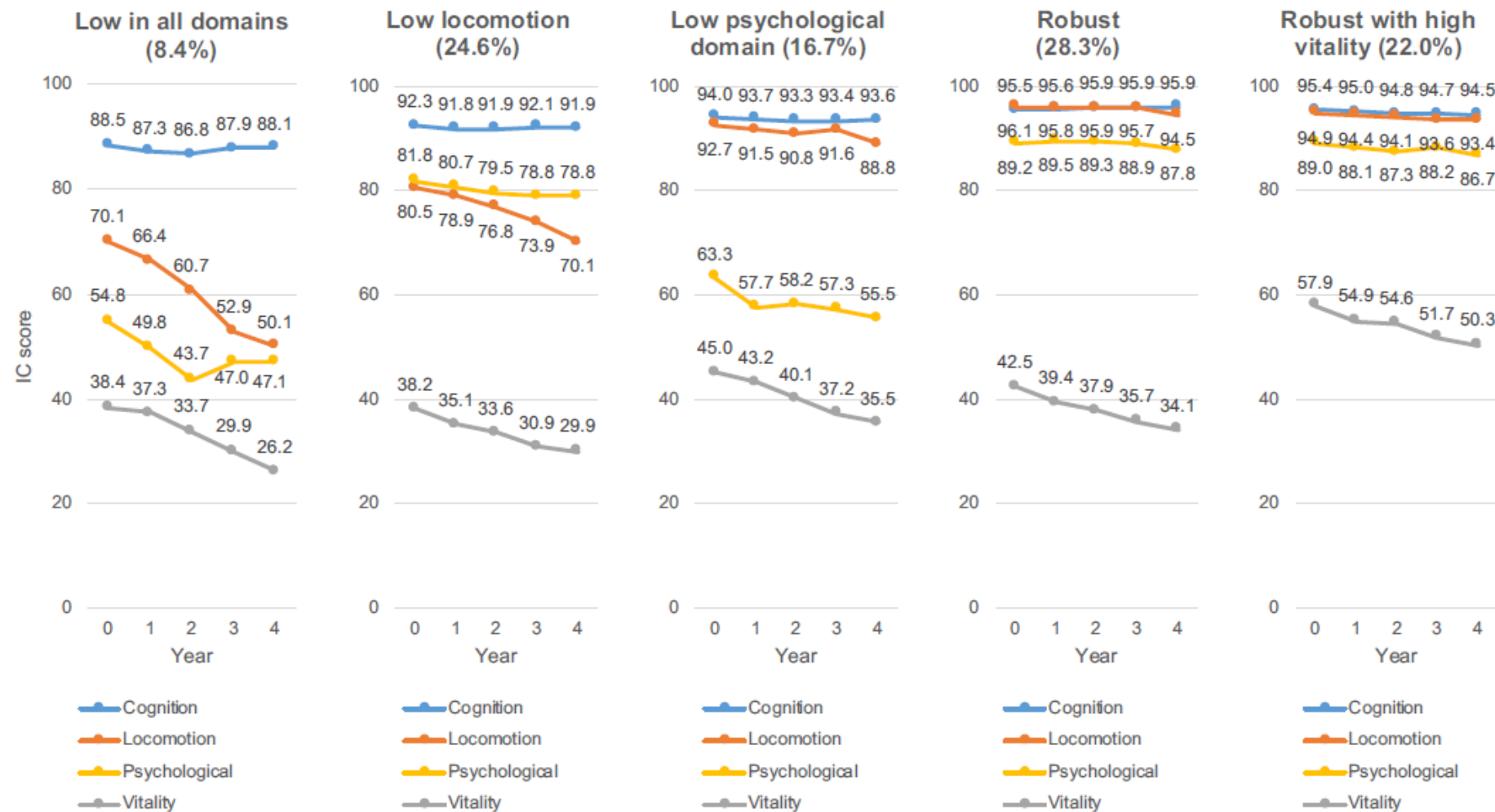
	Low in all domains vs. robust with high vitality		Low locomotion vs. robust with high vitality		Low psychological domain vs. robust with high vitality		Robust vs. robust with high vitality	
	RRR (95% CI)	<i>p</i> value	RRR (95% CI)	<i>p</i> value	RRR (95% CI)	<i>p</i> value	RRR (95% CI)	<i>p</i> value
CRP	1.22 (0.93, 1.60)	0.157	1.20 (0.98, 1.47)	0.084	1.02 (0.82, 1.26)	0.891	0.97 (0.80, 1.18)	0.762
IL-6	1.42 (1.07, 1.88)	0.016	1.37 (1.10, 1.71)	0.005	1.25 (0.99, 1.56)	0.056	1.20 (0.97, 1.48)	0.094
TNFR-1	1.46 (1.09, 1.96)	0.011	1.21 (0.98, 1.51)	0.083	1.06 (0.85, 1.33)	0.579	0.99 (0.81, 1.21)	0.913
MCP-1	0.98 (0.74, 1.29)	0.860	0.91 (0.73, 1.13)	0.381	1.11 (0.90, 1.38)	0.334	0.99 (0.81, 1.21)	0.905
GDF-15	1.99 (1.45, 2.73)	<0.001	1.48 (1.17, 1.89)	0.001	1.29 (1.01, 1.64)	0.044	1.23 (0.98, 1.54)	0.070
ATPase IF1	0.89 (0.66, 1.18)	0.413	0.90 (0.73, 1.11)	0.321	1.05 (0.85, 1.30)	0.664	0.92 (0.76, 1.11)	0.377

All biomarker values were log-transformed and then standardized. All models were adjusted for age, sex, educational levels, MAPT group allocation, and the number of chronic diseases. *CRP*, C-reactive protein; *GDF-15*, growth differentiation factor-15; *IC*, intrinsic capacity; *IF1*, inhibitory factor 1; *IL-6*, interleukin-6; *MCP-1*, monocyte chemoattractant protein-1; *RRR*, relative risk ratio; *TNFR-1*, tumor necrosis factor receptor-1



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Association between aging-related biomarkers and longitudinal trajectories of intrinsic capacity in older adults

Table 1 Characteristics of the study population at the 12-month visit

	Total (<i>n</i> = 1271)	Multi-trajectory group membership					<i>p</i> value
		Low in all domains (<i>n</i> = 107 [8.4%])	Low locomotion (<i>n</i> = 313 [24.6%])	Low psychological domain (<i>n</i> = 212 [16.7%])	Robust (<i>n</i> = 360 [28.3%])	Robust with high vitality (<i>n</i> = 279 [22.0%])	
Age (years)	76.0 (4.3)	78.6 (4.6) ^{a,b,c}	78.0 (4.7) ^{d,e,f}	76.1 (4.1) ^{a,d,g,h}	74.8 (3.6) ^{b,e,g}	74.3 (3.1) ^{c,f,h}	<0.001
Plasma biomarkers							
CRP, mg/L	3.3 (5.3)	4.9 (8.9) ^a	3.6 (5.1)	3.0 (5.0)	3.2 (5.4)	2.8 (3.5) ^a	0.032
IL-6, pg/mL	3.3 (3.1)	3.9 (3.4)	3.6 (2.9)	3.5 (3.9)	3.1 (2.7)	3.0 (3.1)	0.045
TNFR-1, pg/mL	1207.9 (395.1)	1372.6 (497.5) ^{a,b,c}	1276.8 (420.1) ^{d,e}	1192.5 (365.6) ^a	1141.9 (371.1) ^{b,d}	1176.1 (354.7) ^{c,e}	<0.001
MCP-1, pg/mL	220.9 (82.2)	224.3 (75.0)	219.2 (77.6)	229.5 (80.6)	217.9 (86.6)	218.4 (84.9)	0.610
GDF-15, pg/mL	1104.9 (473.1)	1330.4 (507.6) ^{a,b,c}	1200.5 (545.0) ^{d,e}	1106.8 (465.6) ^a	1011.3 (378.2) ^{b,d}	1045.9 (456.0) ^{c,e}	<0.001
ATPase IF1, ng/mL	581.7 (276.6)	586.5 (279.1)	579.3 (274.5)	606.5 (292.6)	581.0 (281.7)	563.9 (258.9)	0.674